ORIGINAL ARTICLE

The Design of the Canadian UnRuptured Endovascular versus Surgery (CURES) Trial

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ABSTRACT: ***Background:*** Once a decision has been made to treat an intact aneurysm, the best treatment remains uncertain. Both surgical and endovascular management strategies are commonly performed for these lesions. Surgical clipping, for years the standard treatment, is gradually becoming supplanted by endovascular treatment. However, there is no randomized data available to compare the results of surgery versus endovascular treatment of unruptured aneurysms (UIAs). ***Methods:*** We report the design of the Canadian UnRuptured Endovascular versus Surgery (CURES) trial to compare angiographic and clinical outcomes following treatment of UIAs. ***Results:*** The Canadian pilot phase will serve two purposes: i) to determine feasibility of the pivotal international study, and ii) to determine the incidence of treatment failure, a composite primary end-point comprising the occurrence of either: failure to accomplish aneurysm obliteration with the initial treatment modality, a major saccular aneurysm remnant or recurrence, or intracranial hemorrhage following treatment at one year. The pivotal international study will address which strategy leads to the best overall clinical outcomes in terms of mortality, morbidity, and clinical efficacy. CURES is designed to be a pragmatic management trial with loose inclusion criteria. The pilot study plans to enroll 260 patients, a size sufficient (at 80% power and 0.05 significance) to detect a decrease in the incidence of treatment failure from 13% to 4%. The formulation of specific hypotheses for the pivotal phase awaits the preliminary CURES morbidity and mortality results. ***Conclusions:*** The CURES trial intends to test surgical versus endovascular management strategies for the treatment of unruptured intracranial aneurysms.

RÉSUMÉ: Le plan de l'essai canadien CURES sur les anévrismes non-rompus: ***Contexte:*** A partir du moment où la décision de traiter un anévrisme non-rompu (ANR) est prise, L'incertitude persiste quant au meilleur traitement. Les traitements chirurgicaux et endovasculaires sont d'utilisation courante. Le clipping chirurgical, le traitement standard pendant de nombreuses années, est graduellement remplacé par le traitement endovasculaire. Cependant il n'existe pas de données d'essais randomisés comparant les résultats de la chirurgie et du traitement endovasculaire des ANRs. ***Méthode:*** Nous décrivons le plan de l'étude CURES, dont l'objectif est de comparer les résultats angiographiques et cliniques suite aux traitements des ANRs. ***Résultats:*** La phase pilote canadienne servira deux fins: 1) estimer la faisabilité de l'essai international pivot et 2) déterminer l'incidence de l'échec de traitement à un an, selon un critère d'évaluation global primaire comprenant soit l'échec de l'oblitération par le traitement initial, un anévrisme résiduel ou récidivant important, ou une hémorragie intracrânienne. L'essai international pivot tentera de déterminer laquelle des deux stratégies mène aux meilleurs résultats cliniques globaux en terme de mortalité, de morbidité et d'efficacité clinique. L'essai CURES est conçu pour être un essai pragmatique avec des critères de sélection larges. L'étude pilote inclura 260 patients, un nombre suffisant (puissance de 80% et seuil de signification statistique de 5%) pour détecter une baisse de l'incidence de l'échec du traitement de 13% à 4%. Les hypothèses spécifiques de l'essai pivot seront énoncées quand les résultats préliminaires de morbidité et de mortalité de CURES seront connus. ***Conclusion:*** L'essai CURES tente d'évaluer le traitements chirurgical et endovasculaire des ANRs.

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The care of patients with unruptured aneurysms has been described as the most vexing scientific question confronting neurosurgeons, neurologists, and neuroradiologists[1]. Once the decision has been made to treat the aneurysm, the best treatment remains uncertain. Surgical clipping, for years considered the gold standard, has recently been challenged by the emergence of endovascular treatment (EVT), a minimally invasive alternative[2-5]. When successful, surgical clipping offers definitive aneurysm exclusion (re-treatment rates as low as 1.5%)[6], with attendant mortality and morbidity estimated at 7-10%[7-9]. In contrast, proponents of EVT have claimed lower treatment-related risks of mortality and morbidity (3-5%)[10,11], at the cost of lower efficacy (20-40% risk of aneurysm recurrence[12,13], with 11.4% requiring re-treatment)[6]. Although the hemorrhage rate from recurrent EVT-treated aneurysms is low (estimated at 0.3-1.1%)[14,15], it is not clearly different from

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the natural history of an unruptured aneurysms in general (assuming 0.9-1.2%/year)[8,16].

Following International Subarachnoid Aneurysm Trial (ISAT), a randomized trial comparing clipping and coiling of ruptured aneurysms, the demonstration of better one year outcomes for ruptured aneurysms treated with EVT has led to a decrease in neurosurgical clipping of not only ruptured but also unruptured aneurysms, particularly in Europe[17]. However, ISAT results should not be applied to unruptured aneurysms (UIAs). First, surgical repair of aneurysms in the setting of subarachnoid hemorrhage (SAH) can be more difficult than for unruptured aneurysms, due to increased cerebral swelling and aneurysm fragility. Second, endovascular treatment of UIAs may involve adjunct techniques and devices, such as stents, that are not frequently used for ruptured aneurysms. The additional risks due to use of these devices[11] may increase the morbidity of EVT. Finally, while short-term benefit can be shown following SAH, for which acute re-bleeding is common, the much lower annual rupture rate of UIAs renders the demonstration of long-term efficacy more problematic, especially for EVT.

Because most patients are asymptomatic, preventive treatments must be very safe. Any less morbid approach would therefore be welcome, and EVT may offer this possibility. However, any risk, no matter how small, must be considered excessive if efficacy cannot be shown. The efficacy of EVT for UIAs has never been proven and is a concern because of aneurysm recurrence following coiling[12,13]. Consequently, many neurosurgeons still rely on surgical clipping to offer life-time protection from rupture. Both treatments are currently used in most centers, and the crucial question is which treatment, when both are available, will lead to the best overall patient outcomes. Many physicians believe that coiling offers a less risky preventive treatment of UIAs than clipping, but this has never been formally proven in a randomized controlled trial (RCT).

Conversely, other physicians believe that surgical clipping offers more frequent, complete occlusion of UIAs than coiling, but this too has never been proven in an RCT. The completeness of occlusion is judged by imaging studies, which, albeit a surrogate, remains an end-point that is widely regarded as a measure of the confidence of protection against future aneurysm rupture. The frequency of major angiographic recurrences after coiling, combined with the lack of definitive proof that peri-operative complications are less with coiling, are the main reasons why many physicians still offer clipping as the first option to patients eligible for coiling. Unfortunately, the results of even large, observational trials such as the ISUIA[18,19], are of insufficient quality to guide clinical decision-making. Only the rigorous methodology of a randomized clinical trial can find a resolution to this problem.

We report the design of the CURES (Canadian UnRuptured aneurysm Surgery versus Endovascular) trial, the first multi-center randomized trial on the management of unruptured intracranial aneurysms.

Overview of Study Design

The CURES trial will be a two-phase trial: the pilot Canadian phase will examine the incidence of treatment failure by one year, using a composite primary end-point which includes anatomic outcomes. The pivotal international phase will be launched if the morbidity and mortality results and recruitment rates obtained in Phase I demonstrate feasibility. Although superior anatomic results following surgery compared to endovascular coiling are expected, this beneficial aspect of surgical clipping has never been demonstrated in a randomized controlled trial. Sufficient numbers (n = 260) could be obtained in Canadian centers alone to complete this pilot phase in a reasonable time-frame.

The comparisons most relevant to patients and physicians, the clinical efficacy and morbidity and mortality of surgical clipping vs. endovascular coiling for unruptured aneurysms, has also never been formally tested using RCT methods. However, it is expected that to demonstrate a significant difference in hard outcomes such as morbidity and mortality will require more patients (estimated n = 1000) than would be difficult to obtain within Canada alone, so the important second phase, if shown to be feasible in the lead-in pilot study, is hoped to expand and include sites outside Canada. The scope of this phase will depend on the projected required number of patients to demonstrate a clinically significant difference between treatment arms, using the CURES randomized morbidity and mortality results.

Primary Hypotheses of CURES

1. Surgical clipping of intradural, saccular, unruptured intracranial aneurysms is superior to endovascular management in terms of decreasing the number of patients experiencing treatment failure from 13 to 4%.

2. An RCT comparing the clinical outcomes of a surgical versus endovascular management strategy is feasible (260 patients can be recruited within four years).

Calculation of Sample Size

A previous systematic review of EVT for UIAs has shown that treatment failures, defined as immediate residual aneurysms and re-treatments during follow-up occurred in 14% and 10% of patients, respectively[20]. Hence, a conservative estimate of treatment failures after EVT is 13% at one year. Treatment failures after surgical treatment has been reported to occur in approximately 2% of cases[6]. With target alpha 0.05 and Power 0.8032, a sample size of 236 patients (118 per group, no losses) would be sufficient to demonstrate a significant difference, using an estimated 3% and 14% treatment failure rates for surgical and endovascular management, respectively, at one year (two-sided Fisher's exact test). Assuming losses at follow-up are less than 10%, we aim to enroll 260 patients in Canada.

End-points – Pilot Phase

The primary end-point of the pilot phase is the incidence of treatment failure, defined as failure of aneurysm obliteration at initial treatment, a major (saccular) angiographic aneurysm remnant or recurrence, or the occurrence of a hemorrhagic event during the follow-up period. Although the anatomic "major" recurrence portion of the primary end-point is a surrogate, it remains an end-point that is widely regarded as measure of the confidence of protection against future aneurysm rupture. The comparison most relevant to patients and clinicians alike, that of morbidity and mortality, would not be possible to achieve with

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Canadian patients alone. Secondary end-points include: the individuated end-points from the composite primary end-point, the incidence of all-cause and treatment-related morbidity (mRS >2) and mortality, and the incidence of peri-treatment hospitalization lasting more than five days, or discharge to a location other than home.

End-points – Pivotal Phase

Without randomized data, it is too early to formulate the specific hypotheses and end-points for the pivotal phase. However, the intent can be expressed as a comparison capturing overall clinical outcomes at a minimum of five years. Preliminary estimates with non-randomized data suggest that at least 1000 patients would be required in order to power a significant result.

Planned Trial Interventions

Surgical clipping or endovascular coiling is performed once for each patient and two or more lesions can be treated at the same sitting. Conservative management of behavioural risk factors (cessation of tobacco and alcohol abuse) and medical treatment of hypertension will be encouraged for both groups for the duration of the study. Treatment will be performed within six weeks of randomization, according to standards of practice, and under general anaesthesia. Details regarding surgical or endovascular technique, type of coils, use of adjunctive techniques such as balloon-remodeling or stents, as well as post-treatment medical management issues, will be left up to the treating physicians. Patients found to have an aneurysm recurrence during the follow-up can be treated, if felt appropriate, but this will be counted as having reached the primary end-point.

Method of Allocation

Patients will be randomly allocated into one of two groups: a) surgical management or b) endovascular management, using a centralized minimization procedure to ensure balance between groups, taking the following patient and aneurysm factors into account: (decreasing hierarchical order) i) age >60, ii) aneurysm size >15 mm, and iii) posterior circulation location.

Inclusion/ Exclusion Criteria

Selection criteria are described in the Table.

Justification of Inclusion and Exclusion and Minimization Criteria

Uncertainty and Equipoise: To be eligible for participation in this trial, the patient must be eligible for both treatment options. Because CURES is a pragmatic trial, we have not attempted to formalize which aneurysms would clearly be better treated with one modality over the other. In the absence of convincing evidence such criteria would be at best arbitrary, and at worst erroneous. The intra and inter-observer agreement in choosing treatment modalities has been shown to be 'fair' in a blinded prospective review of UIA patients treated at one institution[21]. Furthermore, 73% of all patients treated with one or the other option were judged to be eligible for the other treatment option. The process we propose is not to attempt to guess which option would be the best in one particular patient, but to consider the alternative option each time one treatment option is considered. If clipping is being considered, could coiling be a valuable option?, and vice versa. When both options are considered potentially good management strategies, the particular patient can be offered participation in CURES.

Aneurysm and Patient-related Factors

Size: The risk of harbouring an unruptured intracranial aneurysm smaller than 3 mm has been suggested to be low[8], and

Table: CURES inclusion and exclusion criteria

Inclusion Criteria

- Patient at least 18 years-of-age with at least ten years of remaining life expectancy
- At least one documented, never ruptured, intradural, saccular intracranial aneurysm
- The patient and aneurysm are considered appropriate for either surgical or endovascular treatment by the treating team
- Aneurysm size 3-25 mm

Exclusion Criteria

- Patients with any intracranial hemorrhage, including SAH, within the previous 12 months
- Patients with previously incompletely treated intracranial aneurysm
- Lesion characteristics not equally, readily suitable for endovascular or surgical treatment, in the opinion of the physician(s) intending to treat the aneurysm
- Multiple aneurysms, where the treatment plan includes both surgical clipping as well as endovascular coiling
- Aneurysm anticipated (pre-operatively) to require proximal vessel occlusion, a bypass, or other flow-redirecting therapy (including flow-diverter stents) as part of treatment plan
- Patients with baseline mRS >2
- Patients with a single cavernous aneurysm
- Patients with dissecting, fusiform, or mycotic aneurysms
- Patients with arteriovenous malformation
- Pregnant patients (randomization (and treatment) may be delayed until after delivery)
- Patients with absolute contraindications to anaesthesia, endovascular treatment or administration of contrast material, including low-osmolarity agents or gadolinium
- Patients unable to give informed consent

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immediate risks of treatment may not be justified. Furthermore, endovascular treatment of very small lesions is associated with a greater risk of aneurysm perforation[22]. Aneurysms smaller than 3 mm could be followed and then recruited if they enlarge on follow-up. The choice of 25 mm as an upper limit follows from the greater risk of treatment for giant aneurysms, as well as the higher recurrence rate following endovascular treatment of these lesions[23-27]. Giant aneurysms (>25 mm) are rare lesions that commonly require more complex treatment techniques, and may have a different etio-pathogenesis than "routine" aneurysms[28-29]. It is expected that the majority of aneurysms included in this study will be within the more frequent 5-15 mm range. Aneurysm size should be measured using a cross-sectional imaging study, measuring the longest axis of the aneurysm. For partially thrombosed aneurysms, the outer diameter (filling and non-filling portions) of the aneurysm should be measured.

Multiple Aneurysms: Many patients (up to 20-50% in some centers)[30] present with multiple unruptured aneurysms. We would like to include these patients if possible. In order to do our best to ensure that any observed end-points are a result of treatment allocation, we are excluding those patients with multiple aneurysms whose treatment plan includes both clipping and coiling. Patients previously successfully treated for other lesions can be recruited, provided they fit the inclusion and exclusion criteria. When all the aneurysms that will be treated (this need not include all the discovered aneurysms) can be treated with either a surgical management strategy or an endovascular management strategy, those patients can be included in CURES. In this case, the failure to occlude one of the intended aneurysms will be counted as a treatment failure for that modality. The treatment of multiple aneurysms can be staged, both for surgery and for endovascular treatment. These will not be counted as treatment failures.

Posterior Circulation Location: These aneurysms are commonly treated with EVT, but this practice pattern is not uncontroversial, as many posterior circulation aneurysms remain safely treatable by either clipping or coiling. In the spirit of a pragmatic trial, we prefer to leave the judgment as to the eligibility of each patient bearing such aneurysms to the discretion of the treating physician(s).

Patient Age: Patients older than 60 are suspected to tolerate aneurysm treatment (both surgical and endovascular) poorly compared to younger patients[8]. To ensure that this risk factor remains balanced between treatment groups, we have included age > 60 (date of randomization is beyond 60th birthdate) as a minimization criterion.

Patient Follow-up

Patients from both trial arms will be seen in clinic at approximately six weeks as part of routine follow-up care. Patients will be followed with a telephone interview at six months, with another routine clinic visit at one year. These intervals will serve to determine mRS scores, and to inquire regarding possible aneurysm rupture or re-treatment. All patients will have non-invasive imaging (CTA or MRA) at one-year post-treatment to determine the presence of a major, saccular aneurysm recurrence. Non-invasive imaging at one year is considered standard follow-up care of these aneurysms.

Outcome Measures

End-point realization will be determined by the local investigators, with angiographic results sent to the CURES Core Lab for independent review. Outcome measures are detailed below:

Failure of initial treatment is defined as an initial treatment attempt that fails to obliterate the index aneurysm. This end-point will be determined by the treating physician immediately after treatment. Because endovascular treatment sessions conclude with the acquisition of a final series of angiographic images, and not all surgeons obtain immediate post-procedure imaging, there may be a perceived asymmetry of the likelihood that this end-point would be realized between surgery and endovascular. However, a major saccular aneurysm residual left after surgery would still be captured on the one-year imaging study and thus does not constitute a source of bias.

Aneurysm recurrence is defined as a major (saccular) aneurysm remnant or recurrence seen on CTA or MRA performed at one year. Aneurysms treated with clipping are expected to be imaged with CTA, whereas coiled aneurysms will be imaged with MRA due to the coil-related artifact. The relative ability of these imaging modalities to discover small aneurysm residuals remains a contested issue, however, since we are only interested in major, saccular aneurysm recurrences, both types of imaging are equally suitable for this study.

Hemorrhagic event is defined as: 1) cross-sectional imaging (CT or MRI) evidence of intracranial bleeding, or 2) acute headache and lumbar puncture positive for hemorrhage 3) sudden death preceded by severe headache 4) intracranial bleeding proven by post-mortem CT-scanning or autopsy, or 5) unexplained sudden death.

Treatment-related mortality or morbidity is defined as any event occurring within 31 days of treatment leading to mortality or disability (mRS >2).

Planned Analyses

Descriptive statistics will be done on demographic variables and potential risk factors (age, aneurysm size, neck width, multiplicity, smoking status, etc.) to compare the two groups at baseline. Means, standard deviations, and ranges will be presented for quantitative variables such as size of aneurysms and frequency tables for categorical variables (such as the number of patients with multiple aneurysms). Those statistics will be broken down by center and by treatment arm. Comparison of the groups will be assessed through independent ANOVA (quantitative data) or Mantel-Haentzel and χ^2 tests (categorical data). The main statistical test will involve comparisons between the probability of reaching the primary end-point (treatment failure) with a surgical or endovascular management strategy (intent-to-treat analysis). Assuming comparability of groups across centers, the primary outcome (failure of treatment) will be compared between groups using a Fisher's exact test at one year.

Secondary outcomes will be compared between groups using independent t-tests for quantitative variables and χ^2 tests for categorical variables. The analyses of neurological data at follow-up will control for baseline data using logistic regression, ANCOVA or Cox regression multivariate methods. All tests will be interpreted with a 0.05 level of confidence.

Cross Over to the Alternate Treatment Arm

To minimize cross-overs that might occur between randomization and treatment, treatment will be planned to occur within six weeks of randomization. Cross-overs deemed necessary to treat patients (after treatment failures) will of course count as having reached the primary end-point.

Frequency of Analyses

To prevent the alpha spending that follows every additional analysis, the pilot Phase I data will only be analyzed once, after the one 1-year follow-up imaging study has been completed in all participants. Safety data (occurrence of severe adverse events, treatment-related complications, and hemorrhages) will be reviewed periodically by the Data and Safety Monitoring Committee (DSMC) that will meet at on at least a yearly basis. The primary outcome will be assessed at one year.

Stratification of Results

Clinical outcomes will be stratified according to patient age, aneurysm size, and location, with two pre-designated strata for each factor: i) age < 60, and age 60; ii) aneurysm size <15 mm, and aneurysm size 15 mm; and iii) anterior vs. posterior circulation location. Pre-specified stratification of supposed different groups of patients can be required within the context of a pragmatic trial due to the possibility that a beneficial effect seen in one group of patients might be negated by another group with a different response to treatment. The justification for the chosen strata is as follows. Patients older than 60 years-of-age are suspected to tolerate aneurysm treatment (both surgical and endovascular) poorly compared to younger patients[8]. Supposed differences in ease of access to anterior versus posterior circulation aneurysms for surgical clipping or EVT may also lead to differences in treatment outcomes for these two groups of patients[10].

Discussion

The most fundamental clinical dilemma, whether UIAs should be treated or not, will not be addressed by the CURES trial. A previous RCT designed to compare coiling and conservative management, the Trial on Endovascular Aneurysm Management [31] was interrupted due to insufficient recruitment. Because UIAs are routinely treated by clipping or coiling in all neurovascular centers, this trial is designed to address the next important question: Which treatment modality is best for patients with UIAs ?

Large-scale international RCTs are difficult to organize and implement. The financial, regulatory, legal, contractual, and organizational hurdles are so numerous that launching such an effort requires years of hard work, during which time financial support is difficult to secure. Nevertheless, we must attempt to provide our patients with the best possible care in spite of the uncertainty.

What is needed is a large, simple, pragmatic randomized trial that is integrated into clinical practice. Follow-up visits and tests are the same as those performed as a part of routine care. End-points must be pre-defined, simple, meaningful, and resistant to bias. Data can be collected on simple electronic forms. The simplicity of the procedure and lack of extra requirements will help assure that the trial can be performed without extra cost to participating centers. The most significant result, whether patients have better clinical outcomes in the long-run, can only be obtained with a large-scale clinical trial, but we need to start somewhere. Canadian UnRuptured Endovascular versus Surgery was designed to provide a primary hypothesis that can be confirmed or refuted at the end of a pilot phase that is feasible within the network of Canadian centers.

Conclusion

Surgical treatment has long been the accepted standard for effective treatment of unruptured aneurysms, but it may suffer from increased treatment-related morbidity and mortality. Endovascular treatment holds promise as a minimally-invasive alternative, but doubts remain regarding the efficacy and durability of this modality. A randomized clinical trial comparing these two treatments is required to guide and deliver the best possible care to patients harbouring unruptured intracranial aneurysms.

Competing interests

The design of the CURES trial has been reviewed and approved by the Canadian Stroke Consortium. The CURES is registered: ClinicalTrials.gov identifier: NCT01139892.

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